PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 19025.021	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/020751	International filing date (*day/month/year*) 28 June 2004 (28.06.2004)	Priority date (*day/month/year*) 24 May 2004 (24.05.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PTC THERAPEUTICS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 November 2007 (19.11.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Philippe Becamel
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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WASHINGTON, D.C., DC 20004

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*) 06 NOV 2007

Applicant's or agent's file reference
19025.021

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/20751	28 June 2004 (28.06.2004)	24 May 2004 (24.05.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(8): **C12Q 1/68**(2006.01);**C07H 21/04**
USPC: 435/6,69.1,320.1,325;530/350;536/23.5

Applicant

PTC THERAPEUTICS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	15 October 2007 (15.10.2007)	Stephanie K. Mummert, Ph.D.
Facsimile No. (571) 273-3201		Telephone No. 571-272-0872

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/20751

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-27

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/20751

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-27	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-27	NO
Industrial applicability (IA)	Claims 1-27	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US04/20751

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claim Interpretation

The term 'in an absence of SEQ ID NO:4' is being given the broadest reasonable interpretation in light of the specification. The term is not explicitly defined in the spec. Instead, SEQ ID NO:4 is referred to as NeRP and as "SEQ ID NO:4 sets forth a NeRP1, a 336 nucleotide region of a VEGF 5'UTR" (p. 8 of specification) and it is noted that searching the sequence against nucleotide databases does not necessarily provide art where the sequence is deleted. However, the nucleotide boundaries of SEQ ID NO:4 are not established relative to the context of the overall full-length VEGF 5' UTR. Therefore, without clear nucleotide boundaries of the region comprising SEQ ID NO:4, the term is being interpreted as reading on art where the 5' UTR is deleted partially, either at the 5' end of the UTR, the 3' end of the UTR or from the middle.

The term 'UTR having a NeRP1 (SEQ ID NO: 4)' is also being given the broadest reasonable interpretation in light of the specification. As noted above, the limitations of SEQ ID NO:4 are not clearly defined. The term is being interpreted as the opposite of 'in the absence of SEQ ID NO:4' and is interpreted as reading on art where a full length VEGF 5' UTR is present in the nucleotide construct.

The limitations of SEQ ID NO:3 are also not explicitly defined in the spec. Instead, SEQ ID NO:3 is referred to as PTCRE1 and as "SEQ ID NO:3 sets forth a PTCRE1, a 702 nucleotide region of VEGF 5'UTR" (p. 8 of specification) and like SEQ ID NO:4, the nucleotide boundaries of SEQ ID NO:3 are not established relative to the full-length 5' UTR and searching the sequence against nucleotide databases does not necessarily provide art where the sequence is deleted. Therefore, the term 'wherein the PTCRE is not SEQ ID NO:3' is being interpreted as reading on art the term is being interpreted as reading on art where the 5' UTR is partially deleted, either at the 5' end of the UTR, the 3' end of the UTR or from the middle. And where SEQ ID NO:3 is not described either way, or particularly where the sequence comprising 'SEQ ID NO:3, a fragment thereof, or a complement of either' is being interpreted as reading on art where the full length 5' UTR is present in the nucleotide construct.

Claims 1-27 lack novelty under PCT Article 33(2) as being anticipated by Forsythe et al. (Molecular and Cellular Biology, 1996, vol. 16, no. 9, p. 4604-4613). Forsythe teaches a method of analyzing the effect of hypoxia inducible factor on the expression of VEGF (Abstract).

With regard to claims 1-10 and 14, Forsythe teaches a variety of nucleic acid constructs and nucleic acids that comprise a nucleic acid encoding a reporter polypeptide, wherein the nucleic acid sequence encoding a reporter polypeptide is operably linked to a NeRP, said NeRP (SEQ ID NO:4) is operably linked to a PTCRE (wherein said PTCRE is not SEQ ID NO:3), and expression of said reporter polypeptide is capable of being modulated relative to in an absence of said NeRP (Figure 1A, where a variety of constructs comprising deletions of the 5' UTR, and therefore in the absence of SEQ ID NO:3; see also p. 4605, col. 1, 'reporter plasmid constructs'

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

Supplemental Box
In case the space in any of the preceding **boxes is not sufficient.**

heading, where the UTR is linked to luciferase reporter gene).

With regard to claims 11-13 and 15-21, Forsythe teaches a reporter construct wherein said VEGF 5' UTR is in an absence of SEQ ID NO:4 and contains an intron (Figure 1A, where a variety of constructs comprising deletions of the 5' UTR, and therefore in the absence of SEQ ID NO:4; see also p. 4605, col. 1, 'reporter plasmid constructs' heading, where the UTR is linked either to VEGF ORF or luciferase reporter gene), wherein these constructs produce polypeptides (see also p. 4605, col. 1, 'reporter plasmid constructs' heading, where the UTR is linked either to VEGF ORF or luciferase reporter gene), and are produced in vitro (p. 4605, where the constructs are produced in vitro, see 'transient expression assays' heading).

With regard to claims 22-24, Forsythe teaches a nucleic acid molecule that comprises 95-99% sequence identity with a nucleic acid molecule of SEQ ID NO:3, a fragment thereof or a complement of either, consists of SEQ ID NO:3 or a fragment or complement thereof, or consists of a nucleic acid linked to a reporter polypeptide wherein the nucleic acid sequence consists of SEQ ID NO:3 (Figure 1A, where a variety of constructs comprising deletions and full length versions, see KpnI of the 5' UTR, and therefore comprising SEQ ID NO:3).

With regard to claims 23-27, Forsythe teaches a nucleic acid molecule that comprises 95-99% sequence identity with a nucleic acid molecule of SEQ ID NO:4, a fragment thereof or a complement of either, consists of SEQ ID NO:4 or a fragment or complement thereof, or consists of a nucleic acid linked to a reporter polypeptide wherein the nucleic acid sequence consists of SEQ ID NO:4 (Figure 1A, where a variety of constructs comprising deletions and full length versions, see KpnI of the 5' UTR, and therefore comprising SEQ ID NO:4).

Claims 22-27 lack novelty under PCT Article 33(2) as being anticipated by Kamiya et al. (US Patent 6,057,437; May 2000) teach the specific nucleotide sequences of VEGF 3' and 5' UTR regions (Table I, col. 10).

With regard to claims 22-24, Kamiya teaches a nucleic acid molecule that comprises 95-99% sequence identity with a nucleic acid molecule of SEQ ID NO:3, a fragment thereof or a complement of either, consists of SEQ ID NO:3 or a fragment or complement thereof, or consists of a nucleic acid linked to a reporter polypeptide wherein the nucleic acid sequence consists of SEQ ID NO:3 (Table 1, col. 10, see sequence alignment below).

```
Qy        1 TCCAGAGAGAAGTCGAGGAAGAGAGAGACGGGGTCAGAGAGAGCGCGCGGCGTGCGAGC  60
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      337 TCCAGAGAGAAGTCGAGGAAGAGAGAGACGGGGTCAGAGAGAGCGCGCGGCGTGCGAGC  396

Qy       61 AGCGAAAGCGACAGGGGCAAAGTGAGTGACCTGCTTTTTGGGGGTGACCGCCGGAGCGCGG  120
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      397 AGCGAAAGCGACAGGGGCAAAGTGAGTGACCTGCTTTTGGGGGTGACCGCCGGAGCGCGG  456

Qy      121 CGTGAGCCCTCCCCCTTGGGATCCCGCAGCTGACCAGTCGCGCTGACGGACAGACAGACA  180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      457 CGTGAGCCCTCCCCCTTGGGATCCCGCAGCTGACCAGTCGCGCTGACGGACAGACAGACA  516

Qy      181 GACACCGCCCCCAGCCCCAGCTACCACCTCCTCCCCGCCCGCCGCGGCGGACAGTGGACCGCG  240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      517 GACACCGCCCCCAGCCCCAGCTACCACCTCCTCCCCGCCCGCCGCGGCGGACAGTGGACCGCG  576

Qy      241 GCGGCGAGCGCGCGGGCAGGGGCCGGAGCCCGCGCCCGCGAGGCGGGTTGGAGGGGGTCGGG  300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      577 GCGGCGAGCGCGCGGGCAGGGGCCGGAGCCCGCGCCCGCGAGGCGGGTTGGAGGGGGTCGGG  636

Qy      301 GCTGCGCGGCGTCGCACTGAAACTTTTCGTCCAACTTCTCGGGCTGTTCTCGCTTCGGAGGA  360
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      637 GCTCGCGGCGTCGCACTGAAACTTTTCGTCCAACTTCTCGGGCTGTTCTCGCTTCGGAGGA  696

Qy      361 GCCGTGGTCCGCGCGGGGGGAAGCCGAGCCGAGCGAGCCGCGAGAAGTGCTAGCTCGGGC  420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      697 GCCGTGGTCCGCGCGGGGGGAAGCCGAGCCGAGCGAGCCGCGAGAAGTGCTAGCTCGGGC  756

Qy      421 CGGGAGAACCGCAGCCGGAGGAGCGGGAGGAGGAAGAAGAGAAGGAAGAAGAAGAAGGGGG  480
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      757 CGGGAGGAGCCGCAGCCGGAGGAGCGGGAGGAGGAAGAAGAGAAGGAAGAAGAAGAAGGGGG  816

Qy      481 CCGCAGTGGCGACTCGGCGCTCGGAAGCCGGGCTCATGGACGGGTGAGGCCGCGGTGTGC  540
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      817 CCGCAGTGGCGACTCGGCGCTCGGAAGCCGGGCTCATGGACGGGTGAGGCCGCGGTGTGC  876

Qy      541 GCAGACAGTGCTCCAGCCGGCGCGCGCTCCCCAGCCCTGGCCCGGGCTCCGGCCCGGGGA  600
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      877 GCAGACAGTGCTCCAGCCGGCGCGCGCTCCCCAGCCCTGGCCCGGGCTCCGGCCCGGGGA  936

Qy      601 GGAAGAGTAGCTCGCCGAGCGCCCGAGGAGAGCGGGCCGCCCCACAGCCCGAGCCGGAGA  660
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      937 GGAAGAGTAGCTCGCCGAGCGCCCGAGGAGAGCGGGCCGCCCCACAGCCCGAGCCGGAGA  996
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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

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Qy      661 GGGAGCGCGAGCCGCCCGGCCCGGTCGGGCCTCCGAAACC 702
            ||||||||||||||||||||||||||||||||||||||||||
Db      997 GGGAGCGCGAGCCGCCCGGCCCGGTCGGGCCTCCGAAACC 1038
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With regard to claims 23-27, Kamiya teaches a nucleic acid molecule that comprises 95-99% sequence identity with a nucleic acid molecule of SEQ ID NO:4, a fragment thereof or a complement of either, consists of SEQ ID NO:4 or a fragment or complement thereof, or consists of a nucleic acid linked to a reporter polypeptide wherein the nucleic acid sequence consists of SEQ ID NO:4 (Table 1, col. 10, see sequence alignment below).

```
Qy        1 TCGCGGAGGCTTGGGGCAGCCGGGTAGCTCGGAGGTCGTGGCGCTGGGGGCTAGCACCAG 60
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        1 TCGCGGAGGCTTGGGGCAGCCGGGTAGCTCGGAGGTCGTGGCGCTGGGGGCTAGCACCAG 60

Qy       61 CGCTCTGTCGGGAGGCGCAGCGGTTAGGTGGACCGGTCAGCGGACTCACCGGCCAGGGCG 120
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       61 CGCTCTGTCGGGAGGCGCAGCGGTTAGGTGGACCGGTCAGCGGACTCACCGGCCAGGGCG 120

Qy      121 CTCGGTGCTGGAATTTGATATTCATTGATCCGGGTTTTATCCCTCTTCTTTTTTCTTAAA 180
            ||||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db      121 CTCGGTGCTGGAATTTGATATTCATTGATCCGGGTTTTATCCCTCTTCTTTTTTCTTAAA 180

Qy      181 CATTTTTTTTTAAAACTGTATTGTTTCTCGTTTTAATTTATTTTGCTGCCATTCCCCA 240
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      181 CATTTTTTTTTAAAACTGTATTGTTTCTCGTTTTAATTTATTTTGCTGCCATTCCCCA 240

Qy      241 CTTGAATCGGGCCGACGGCTTGGGGAGATTGCTCTACTTCCCCAAATCACTGTGGATTTT 300
            ||||||||||| |||||||||||||||||||||||||||||||||||||||||||||||||
Db      241 CTTGAATCGGGCCGACGGCTTGGGGAGATTGCTCTACTTCCCCAAATCACTGTGGATTTT 300

Qy      301 GGAAACCAGCAGAAAGAGGAAAGAGGTAGCAAGAGC 336
            |||||||||||||||||||||||||||||||||||||
Db      301 GGAAACCAGCAGAAAGAGGAAAGAGGTAGCAAGAGC 336
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Claims 1-27 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.